PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Kazumi DANJO, et al.

Appln. No.: 10/560,169

Confirmation No.: 9404

Filed: December 9, 2005

Docket No: Q91343

Group Art Unit: 1619

Examiner: Ivan A. Greene

For: RADIAL SPHERICAL CRYSTALLIZATION PRODUCT, PROCESS FOR PRODUCING THE SAME, AND DRY POWDER PREPARATION CONTAINING THE CRYSTALLIZATION PRODUCT

SUBMISSION OF EXECUTED DECLARATION UNDER 37 C.F.R. §1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Submitted herewith is a copy of an executed Declaration Under 37 C.F.R. §1.132 signed by Takeaki Furudate.

Respectfully submitted,

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Date: May 7, 2009

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DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Takeaki Furudate, hereby declare and state:

I am a citizen of JAPAN.

I received a Masters degree in Engineering from the Department of Chemistry and Biotechnology, in 2000, from The University of Tokyo in Japan.

I have been employed by Taisho Pharmaceutical Co., Ltd. since 2004.

I am a co-inventor of the invention described and claimed in the above-identified application.

I am familiar with the prosecution of this application. I have reviewed the Office Action dated January 7, 2009, and the rejections of the claims set forth therein. Specifically, I understand that claims 1, 3-5 and 8-12 have been rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,063,138 to Hanna et al. ("Hanna"). I also understand that claims 1, 3-5 and 9-12 have been rejected under 35 U.S.C. § 102(b) as being anticipated by the article by Reverchon et al., as published in Powder Technology, 114 (2001), pp. 17-22 ("Reverchon"). I further understand that claims 1-5, 8-12 and 20-21 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hanna, Reverchon, U.S. Patent No. 5,975,076 to Yianneskis et al. ("Yianneskis"), and U.S. Patent No. 5,192,528 to Radhakrishnan et al. ("Radhakrishnan").

Comparative Experiment

The following comparative experiment was conducted by me or under my supervision in order to support the patentability of the radial spherical crystallization product as claimed in the above-captioned application, over Hanna and Reverchon, Yianneskis and Radhakrishnan.

1. Object of the Experiment

The object of the experiment is to show that the present radical spherical crystallization product as recited in the present claims has unexpectedly superior properties as compared to the product of Hanna, which I consider to be the closest specifically disclosed product of the cited references.

2. Test Methods

In the present Experiment, similar techniques to those set forth in Example 2 of the present specification were used to prepare the radial spherical crystallized product of the present claims. See present specification at page 19, line 13 to page 20, line 19. In Example 2, the inhalation properties of a radical spherical crystallization product made of lactose and mixed with salbutamol sulfate (Preparation 1 of the present invention) were compared to the inhalation properties of a commercially available lactose LI-1200 (Comparative Product 1). The products were encased in gelatin capsules. An e-haler was used as the inhalation device. The e-haler was attached to an Andersen cascade impactor (ACI) through a mouthpiece, and the contents were inhaled using a vacuum pump. After the inhalation, an inhalation characteristics evaluation test was conducted. That is, the amount of salbutamol sulfate of the preparation deposited on each fraction was assayed in order to determine the ratio of the amount of preparation transported to the lung to the amount filled in the capsule. See Table 6 in the present specification at page 20.

In the present Experiment, a radial spherical crystallization product was prepared by the method of the present invention and by the method disclosed in Hanna. The crystallization products were encased in gelatin capsules. A jet-haler was used as the inhalation device. The jet-haler was attached to an Andersen cascade impactor (ACI) through a mouthpiece. The inhalation characteristics evaluation test was conducted in a similar manner as discussed above with respect to Example 2. The experiment shows that the method of making the products greatly affects the inhalation characteristics of the products.

3. **Manufacturing method of a crystallization product (lactose) similar to Hanna's product**

In order to prepare the crystallized product by the method of Hanna, I carried out the following steps. The carbon dioxide supply pump was turned on and once the pump was cooled to -5°C, the back pressure regulator was turned on, the pressure and temperature were set, the carbon dioxide pass valve and the main stopcock of the carbon dioxide tank were opened, and the carbon dioxide supply switch was turned on to start supply of the carbon dioxide. Once the pressure reached the set value, the sample component supply pump was set, and the sample component supply switch was turned on to start the supply of the sample component. Once the pressure in the sample component supply pump reached the set value, the sample component pass valve and the ethanol pass valve were opened to start the supply of the sample and the ethanol. After stabilization of the inside of the vessel, the sample component was introduced into the vessel from the inject port of the sample, thereby initiating crystallization. After crystallization was completed, the sample component supply and ethanol supply pumps were turned off, the valves were shut, and carbon dioxide was supplied for 30 minutes or more to dry the inside of the column. Next, after turning off the carbon dioxide pump and closing the main stopcock to the carbon dioxide tank, the pressure provided by the back pressure regulator was gradually reduced. Finally, the exhaust valve was opened, the inside of the vessel was completely returned to normal pressure, and the crystallization product was collected from the inside of the column. The crystallization conditions are shown below in TABLE 1.

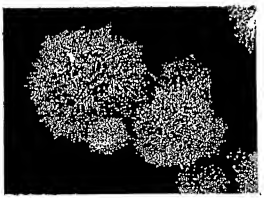
TABLE 1

Operation	Conditions
CO_2 flow rate (ml/min)	14
EtOH flow rate (ml/min)	3.5
Sample component solution flow rate (ml/min)	0.020
Pressure (MPa)	25
Temperature (°C)	70
Concentration of lactose solution (% w/w)	20

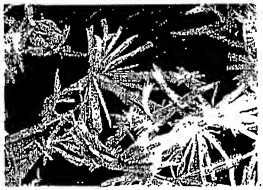
4. Observation of Particle Formation

The particle formation of the product according to the present invention and of the product similar to Hanna's product were observed through a Scanning Electron Microscope (SEM). The respective products are shown below.

A radial spherical crystallization product of the present invention (lactose):



A crystallization product similar to Hanna' s product (lactose):



5. **Release rate (%) from jet-haler device**

Next, the release rate (%) of the crystallization products obtained were determined. To determine the release rate, the total amount of crystallization product encased in capsules before inhalation was compared to the total amount of crystallization product that remained in the device and capsules after inhalation, as further described below.

10 Mg of the radial spherical crystallization product of the present invention and 10 mg of the crystallization product similar to Hanna's product were encased in gelatin capsules. Four capsules for each product were prepared. A jet-haler was used as the inhalation device. The jet-haler was attached to an Andersen cascade impactor (ACI) through a mouthpiece and the capsules including the radial spherical crystallization product of the present invention were charged into the jet-haler. Likewise, the crystallization product similar to Hanna's product were similarly charged. After preparing for inhalation in accordance with the manual of the jet-haler, the contents were inhaled for 5 seconds at a rate of 28.3 l/min using a vacuum pump. The

inhalation was conducted three times (approximately 10 mg of product per capsule, and there were a total of four capsules per product).

The release of a crystallization product was calculated by subtracting (B) the amount of a crystallization product originally encased remaining in the devices and capsules after inhaling from (A) the amount of a crystallization product in the capsules. A release rate (%) was obtained by dividing the release of the crystallization product: (A) - (B) by the amount of a crystallization product encased in the capsules: (A). The formula for calculating the release rate (%) is as follows: Release rate (%) = ((A) (B)) / (A) x 100.

The following TABLE 2 shows, for the product according to the present invention and the product according to the method of Hanna, the amount of crystallization product originally encased in the capsules before inhalation, and the amount remaining after inhalation.

TABLE 2.

	Starting total amount of crystallization product filled into the capsules (mg) (4 capsules for each experiment, each capsule having 10 mg of product)	Ending total amount of crystallization product remaining in the devices and capsules after inhaling (mg)	Release rate
Crystallization product of the present invention (lactose)	40.62	6.01	85.2
Crystallization product amended Hanna approach (lactose)	40.52	24.98	38.4

6. Conclusion

Because the radiated parts of a crystallization product similar to Hanna's product (lactose) are long in length, the particles become tangled with each other in a complicated manner and have relatively-strong aggregation, thereby aggregating into large masses. Thus, when the product is exposed to force from the flow of inhalation, the aggregated particles become more compacted and it becomes difficult to release the particles from the capsules.

On the other hand, the radiated parts of a radical spherical crystallization product according to the present invention are relatively-short in length. Therefore, when the product is exposed to force from the flow of inhalation, the aggregated particles become loose easily and the particles are readily released from the capsules.

This is shown by the results set forth in TABLE 2, which show that the release rate of the product of Hanna (38.4%) is much lower than the release rate of the product of the present invention (85.2%), and supports the unexpected superior properties of the presently claimed radial crystallization product.

As the above results are mainly caused by the method of making of the crystallization product, the crystallization product formed from a drug carrier and the crystallization product formed from a drug substance, such as salbutamol, may be expected to yield similar results. The method of making the crystallization product of the present invention is completely different from the method of making Hanna's product or Reverchon's product. Thus, in my opinion, the test data shows that the products of the cited references and of the present invention are different, and that the radial spherical crystallization products of the present invention have

unexpectedly superior inhalation properties over the inhalation properties of the products of the cited references.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: May 7, 2009

Takeaki Furudate
Takeaki Furudate